Post COVID-19 Sino-Orbital Mucormycosis: A Therapeutic Challenge

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ABSTRACT

Objective: To determine the frequency of sino-orbital mucormycosis outcomes in diagnosed patients of COVID-19 and its association with the duration of the disease.

Study Design: Case series**.**

Place and Duration of Study: Armed Forces Institute of Ophthalmology, Pak Emirates Military Hospital, Rawalpindi, from Feb to Jul 2021.

Methodology: A sample size of 20 was calculated using WHO calculator. Diagnosed patients of COVID-19 who fulfilled the inclusion criteria were selected through consecutive sampling technique. The mode of presentation, in-depth imaging findings, associated co-morbidities and management/follow up details were collected.

Results: Total 20 patients were included in study. There were 12 (60%) male and 8 (40%) female. Mean age of patients was 60.4 ± 9.8 years. Outcomes of study were treatment, still of follow up, mortality and mortality with sepsis, survival and exenteration (15%, 15%, 25%, 5%, 25% 15% respectively). Among all the patients, 2(10%) patients showed intraconal and extra-conal orbital involvement, 9 (45%) showed left, 8 (40%) showed right and 1(5%) showed both orbits involvement. Outcomes of sino-orbital mucormycosis showed significant association with COVID-19 duration (p=0.03).

Conclusion: Sino-Orbital mucormycosis is a common and potentially life-threatening complication of COVID-19. Early initiation of anti-fungal treatment as well as surgical intervention are key to decrease both the mortality and morbidity associated with the disease.

Keywords: Coronavirus disease, Invasive fungal sinusitis, Sino-orbital mucormycosis.

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INTRODUCTION

Globally, novel coronavirus disease (COVID-19) has been declared a pandemic and remains a serious public health challenge.[1] COVID-19 is caused by SARS-CoV-2 that is an enveloped, positive, single stranded 29.9, RNA beta virus. The first case of COVID-19 was reported in Wuhan, China in December 2019. Later on the disease rapidly disseminated around the world and the World Health Organization (WHO) declared it apandemic on 11th March, 2020.[2] An estimated 223 countries are affected with COVID-19 with 138 million cases and 2.9 million mortalities reported globally.[3] In the United Stated, COVID-19 is the third leading cause of mortality following cardiovascular disease and cancer.[4] However, WHO reported global case fatality rate 2.2% for COVID-19 as current estimate. WHO reported 873,220 confirmed cases of COVID-19 and 19,384 confirmed deaths in Pakistan in May 2021.

The initial symptoms of COVID-19 include fever, shortness of breath, dry cough, tachypnea, diarrhea, chest pain, vomiting, confusion, nasal congestion, sore throat, dyspepsia, sneezing, sputum production, viral conjunctivitis, discoloration of fingers or toes and ansomia.[5]

Mucormycosis infection of the para-nasal sinuses is a life-threatening complication of the disease. The disease mainly affects immunocompromised patients who have an impaired neutrophilic response. Patients with hematological malignancies, uncontrolled diabetes mellitus, iatrogenic immunosuppression and acquired immunodeficiency syndrome are at high risk of developing mucormycosis infection of sinuses.[6]

COVID-19 infection is associated with a wide range of illness patterns it may vary frommild cough to life threatening pneumonia.[9] Several studies have documented different manifestations and complications associated with COVID-19. Moreover, new cases are emerging with the passage of time and Health care workers and researchers are learning more about this novel COVID-19 pandemic.[10] Globally, mucormycosis incidence varies from 0.005 -1.7/million population. However, prevalence of mucormycosis in India is 0.14/1000 (eighty times higher that developing world). Globally, mucormycosisfatality rate is 46%. Evidence suggests that orbital involvement increases fatality rate

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50-80%. Tissue necrosis is hallmark of mucormycosis and often a late sign.[7]

The objective of the study was to determine the frequency of sino-orbital mucormycosis outcomes in diagnose patients of Covid-19 and its association with the duration of the disease.

METHODOLOGY

A case series was conducted at Armed Forces Institute of Ophthalmology, Pak Emirates Military Hospital, Rawalpindi, from February to July 2021. A sample size of 20 patientswas calculated using WHO calculator with frequency of affected maxillary sinuses 3%,[8] confidence interval 95% and absolute precision 7%. Patients were selected through consecutive sampling. Ethical approval was taken from respective ethics board of hospital. Inclusion criteria of study was age more than 18 years, radiological (HRCT) evidence of COVID-19 pneumonia, histopathologic evidence of rhino-orbital cerebral mucormycosis and patients requiring supplementary oxygen/steroids along with conventional COVID-19 treatment. Exclusion criteria was based upon patients who did not require hospitalization for COVID-19, patients who did not require supplementary oxygen/steroids during their hospital stay and lack of histopathologic evidence of mucor mycosis.

The details of patient presentation, radiological findings, any associated comorbid and management plan were collected. Treatment with intravenous amphotericin-B was initiated in those who fulfilled the inclusion criteria. This was followed by surgical debridement of the orbit as well as the involved sinuses in collaboration with the otolaryngorhinology department.

Data was analyzed using Statistical Package for the Social Sciences (SPSS) version 24. Descriptive statistics were reported as frequency, percentage, mean and standard deviation. Inferential statistics were reported with the help of Fisher's exact test. The *p*-value of ≤0.05 was considered statistically significant.

RESULTS

Total 20 patients were included in study. There were 12 (60%) male and 8 (40%) female. Mean age of patients was 60.4 ± 9.8 years. There were 10 (50%) patients in age group 40-60 years and 10 (50%) patients in age group 61-80 years. In our data, 3 (15%) patients had controlled diabeties mellitus while 17(85%) had uncontrolled diabetes mellitus. Among all the patients, 14 (70%) were hypertensive while 6 (30%) were non hypertensive. Among all the patients 6 (30%) had ischemic heart disease (IHD) while 14 (70%) did not had IHD. Only one patient had breast cancer as other co morbidity. Visual acuity was counting figure in 3 (15%), hand movement 5 (25%), perception of light in 3 (15%) and no perception of light 9 (45%). Frontal, Maxillary, Ethmoid and sphenoid sinus affected were shown in Table-I.

Table-I: Frequency of affected sinus

Sinus Affected							
Frontal		**Maxillary**		**Ethmoid**		**Sphenoid**	
Right	7 (35%)	Right	9 (45%)	Right	1 (5%)	Right	3 (15%)
Left	3 (15%)	Left	6 (30%)	Left	3 (15%)	Left	4 (20%)
Both	2 (10%)	Both	2 (10%)	Both	4 (20%)	Both	-

In our data, among all the patients, 2 (10%) patients showed intraconal and extra-conal orbital involvement, 9 (45%) showed left, 8 (40%) showed right and 1 (5%) showed both orbits involvement as shown in Table-II.

Table-II: Spread of mucormycosis.

Spread					
Intra-Orbital		**Intra-Cranial**		**Palate**	
Intra-conal and extra-conal	2 (10%)	No	19 (95%)	No	16 (80%)
Left orbits	9 (45%)	Yes	1 (5%)	Yes	4 (20%)
Right Orbits	8 (40%)				
Both orbits	1 (5%)				

Outcomes of study were treatment, still of follow up, mortality and mortality with sepsis, survival and exenteration 3 (15%), 3 (15%), 5 (25%), 1 (5%), 5 (25%) and 3 (15%) respectively)as shown in Figure-1. Intra orbital involvement mucormycosis (coronal section) and intra orbital involvement in mucormycosis (axial section) are shown in Figure-2 and Figure-3.

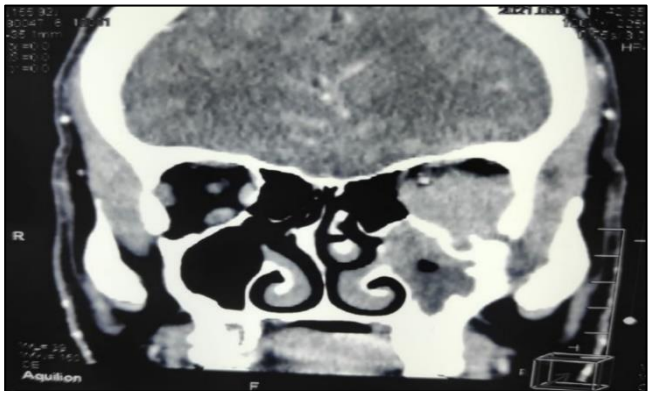

Figure-1: Outcomes of sino-orbital mucormycosis.

Outcomes of sino-orbital mucormycosis showed insignificant association with duration of COVID-19 (*p*=0.345) as shown in Table-III.

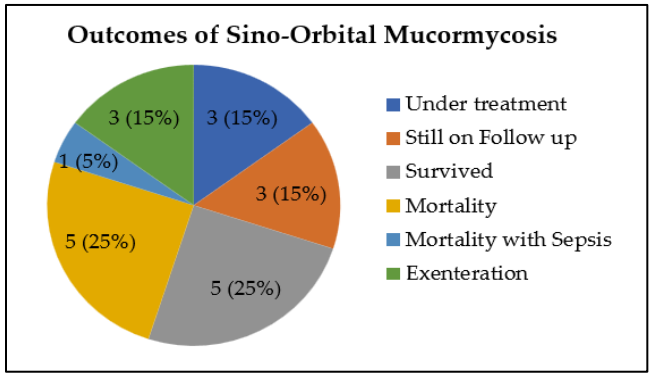

Figure-2: intra-orbital involvement in mucormycosis (coronal section).

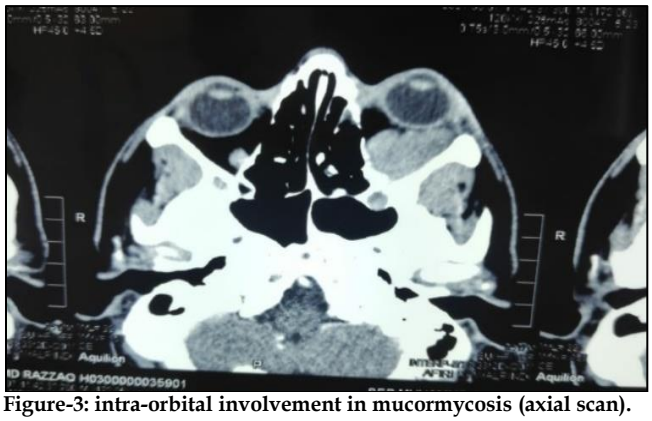

Figure-3: intra-orbital involvement in mucormycosis (axial scan).

orbit spread. First investigation is usually done with non-contrast computed tomography while MRI is recommended if the fungal infection is suspected to extended in intra-cranial or intra-orbital region.[13]

In present study, among all the patients, 10% patients showed intraconal and extra-conal orbital involvement, 45% showed left, 40% showed right and 5% showed both orbits involvement. Outcomes of sino-orbital mucormycosis showed significant association with COVID-19 duration (p=0.03).

Monte *et al,* reported a COVID-19 case associated with sino-orbital mucormycosis showed that the disease generally developed as a result of immunosuppression. They explain that mold gets entry through respiratory tract to more progression towards orbital and intracranial structures (in head and neck case). However, good prognosis of this disease requires early diagnosis and management.[14] A similar case report of 60-year-old man with rhino-orbital mucormycosis and associated COVID-19 showed with positive reverse transcriptase polymerase chain reaction (RT-PCR) and admitted for treatment. Over the duration of admission, the patients show signs of orbital cellulitis. MRI showed soft tissue swelling of malar, premaxillary, right pre-septal and regions of retrobulbar area with paranasal sinusitis. They suggested that physician

Table III: Association of outcomes of Sino-Orbital Mucormycosis and duration of COVID-19

Duration of COVID Disease	Outcomes of Sino-Orbital Mucormycosis						*p*-value
	Under Treatment	Still on Follow up	Survived	Death	Death with Sepsis	Exentration	
≤3 months	-	-	1 (5.0%)	2 (10%)	1 (5%)	1 (5%)	0.345
>3 months	3 (15%)	3(15%)	4 (20%)	3 (15%)	-	2 (10%)	
Total	3 (15%)	3(15%)	5 (25%)	5 (25%)	1 (5%)	3 (15%)	

DISCUSSION

In present study, outcomes of sino-orbital mucormycosis were treatment, still of follow up, mortality and mortality with sepsis, survival and exenteration (15%, 15%, 25%, 5%, 25% 15% respectively) in COVID-19 patients.Mucor mycosis was described by Paltaud in 1885 as an aggressive fungal infection that affects patients by alteration of their immunological system. Presentation of this lethal fungal disease with rhino cerebralinfectionis very common in different countries.[11] Previously the incidence of mucor-mycosis was very low (0.005/1.7 million population) but this has seen a sharp rise with the emergence of the COVID-19 pandemic. Mucor is a saprophytic fungus. Due to low virulence of mucor, it may be present in nasal mucosa.[12] Due to immunosuppression, fungus germinates in paranasal sinus resulting in intra-cranial and intra-

must be aware of invasive fungal infection secondary to coronavirus disease.[15] Werthman-Ehrenreich reported that a 33-year-old woman was presented with COVID-19, proptosis and altered mental status. Later on she was diagnosed with orbital compartment mucormycosis along with COVID-19.[16]

Evidence exist that there are several reasons for association of COVID-19 and immunosuppressive disease process.[17] Some studies reported that during COVID-19 admission, more use of broad spectrum antibiotics and steroids for COVID-19 treatment leads to exacerbation of preexisting fungal infection.[18] Safi *et al,* reported that incidence of invasive fungal infection with COVID-19 is 26.7%.[19] On April 2020, Gupta *et al,* a high proportion of patients recovered from COVID-19 are at high risk of developing fungal invasive disease.[20] Another similar study reported that 8% of COVID-19 patients recovered from diseases are more prone to

have fungal infections due to more use of steroids and antibiotics.[21]

Surgical debridement of fungal infected area is usually possible after confirmation of diagnosis. Surgical treatment of disease is not based upon curative aim; however, the aggressive surgery is important for survival of patients. Moreover, the prognosis of disease remained poor ever after surgical treatment.[22]

To the knowledge of the authors, this is the first study done on the local population that aimed to uncover the relationship between both the incidence of sino-orbital mucor mycosis in diagnosed patients of COVID-19 as well as its association with the duration of the disease. It is recommended that further studies be carried out since sino-orbital mucor mycosis has a high mortality rate. Early surgical as well as medical intervention may be the key to increasing the chances of patient survival.

LIMITATION OF STUDY

Our study design seemed to be week for evaluation of in depth findings of sino-orbital mucormycosis. Cohort study design with long duration of follow up is required for in depth finding. Another limitation was only radiological diagnosed patients reporting to a specialty clinic were included in the study. The effect of the co-morbids that these patients suffered from on the duration of the disease was not accounted for. Also, there was a lack of uniformity in the treatment protocols offered to the patients.

LIMITATIONS OF THE STUDY

The limitations of our study included a small sample size and a lack of standardization of treatment protocols.

CONCLUSION

Sino-orbital mucormycosis is a serious complication of COVID-19 that may involve any of the paranasal sinuses. Early surgical intervention as well as initiation of systemic anti-fungals are empirical for the reduction of both the mortality and morbidity associated with the disease.

Conflict of Interest: None.

Authors' Contribution

MA: Data collection, MS: Manuscript writing, MA: Manuscript writing, SAHN: Statistical analysis, MUG: Data collection, UI: Manuscript writing.

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